

P311 Downregulates TGF- β 1 and TGF- β 2 Expression but not TGF- β 3 During Myofibroblast Transformation

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We identified P311 by screening for genes differentially expressed during smooth muscle myogenesis. P311, also referred to as PTZ17, is an 8-kDa protein previously found in neurons and muscle. P311 does not belong to any known family of proteins and its function remains largely undetermined. P311 has a conserved PEST domain (sequences rich in Pro, Glu, Ser and Thr) which serves as a rapid degradation signal for the ubiquitin/proteasome system. We recently showed that expression of P311 in fibroblast cell lines NIH-3T3 and 10T1/2 induced phenotypic changes consistent with myofibroblast transformation (Pan et al. *submitted*). The P311-induced changes differed however from the well-characterized fibrogenic myofibroblast phenotype in that P311 inhibited expression of TGF- β 1, TGF receptor II and TGF- β 1-activating MMP-2, with the resultant decrease in collagen expression. This further study on the three TGF- β s confirmed that during myofibroblast transformation P311 downregulates TGF- β 1 expression. In addition we found that P311 inhibited TGF- β 2 mRNA but it had no effect on TGF- β 3 message. Deletion of the PEST domain (P311 Δ PEST) reversed the effect of P311 on TGF- β isoforms. P311 Δ PEST upregulated TGF- β 1 and TGF- β 2 mRNA while TGF- β 3 mRNA levels decreased. Furthermore, we found that P311 interacts with TGF- β 2 in a yeast two hybrid system through a sequence conserved among the three TGF- β species. P311-TGF- β 2 interaction was confirmed by glutathione-S-transferase pull-down studies. Using this assay we determined that P311 also interacts with TGF- β 1 but not with TGF- β 3. Our studies therefore suggest that P311 modulates TGF- β by acting at several levels of regulation and involves participation of its PEST domain.